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Review of Pharmaceutical Controlled Release Methods and Devices.

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1. Introduction.

An example of the utilisation of latex coatings is by the pharmaceutical industry, in the preparation of drug coatings, and industries where similar technology may be employed in dispersion systems that might previously have relied on the periodic addition of a chemical. The aim of this Page is to introduce some of the ideas from the literature for the designs of various (controlled) release methods.

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2. Polymers and the Pharmaceutical Industry.

Polymers have gained in importance in the pharmaceutical industry as both drug encapsulants and vehicles of drug carriage: either protecting an active agent during its passage through the body (or in storage by preventing moisture ingress [Udeala & Aly (1989)]) until its release, or controlling its release. A conventional (*eg*, sugar) tablet coating has the disadvantageous side effect of delivering what may be an initially too high and, hence, harmful, dose of active agent (typically, drug is rapidly released from its dosage form, reaching a maximum concentration, which then decays exponentially until the next administration), to regions of the body where the drug may not be at its most effective; when the general aim of any medication is to generate a response in a specific area or organ of the body requiring treatment. These problems can be overcome to some extent by sustained/retarded release, and/or selective delivery of the drug to the targeted organs [*eg*, Gardner (1983), Gregoriadis (3 references: 1977, 1986, 1988), Poznansky & Juliano (1984), Tomlinson & Davis (1986)]. **Advantages of controlled release** devices thus possibly include: delivery to the required site; delivery at the required rate; fewer applications; reduced dangers of overdose, or side effects; and also economic advantages by virtue of more efficient dosage, at the expense of possibly more complicated fabrication. Much of the relevant literature is very precise in that it either concentrates, for example, on a specific type of polymer offering suitable transport characteristics for an individual permeant, or concentrates on a range of permeants transported through a single polymer type, or concentrates on a unique application.

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3. Drug Delivery.

In recent years, there have been numerous developments in polymeric carriers and controlled release systems (some commercially available devices have been described by Lonsdale (1982)). A few examples mentioned in the literature include:

- films with the drug *in* a **polymer matrix** [*eg*, Davis & Illum (1988), Douglas *et al.* (1987), Oppenheim (1981)] (**monolithic devices**);
- the drug contained *by* the polymer (**reservoir devices**) [*eg*, Lehmann *et al.* (1979)];
- polymeric colloidal particles or microencapsulates (**microparticles, microspheres** or **nanoparticles**) in the form of reservoir and matrix devices [*eg*, Douglas *et al.* (1987), Oppenheim (1981)];
- drug contained by a polymer containing a **hydrophilic** and/or **leachable additive** *eg*, a second polymer, surfactant or plasticiser, etc. to give a porous device, or a device in which the drug release may be osmotically 'controlled' (both reservoir and matrix devices) [*eg*, Fites *et al.* (1970), Muhammad *et al.* (1991), Samuelov *et al.* (1979), Zentner *et al.* (1985)];
- **enteric coatings** (ionise and dissolve at a suitable pH) [*eg*, Muhammad *et al.* (1991)];
- (soluble) polymers with (covalently) attached **'pendant' drug** molecules [Chafi *et al.* (3 references: 1988, 1991 & 1992), Duncan & Kopacek (1984), Scholsky & Fitch (1986)];
- devices where release rate is controlled dynamically: *eg*, the **osmotic pump** [Theeuwes (1975)].

More recently, speculation in the literature has centred around the possibility of using the recently discovered large cage-like molecules such as the C_{60} Buckminster-fullerenes [Culotta & Koshland (1991)] (**'Buckyballs'**) (1985 [Taubes (1991)]), or hyperbranched (starburst) dendrimers [Alper (1991)] (late 1970s). The latter are large,

350,000 molecular weight, uniform, hollow, polymer spheres with a surface area comparable to that of carbon black (1,000 $m^2 g^{-1}$). Some of these hyperbranched dendrimers are even water soluble.

Ideally, the delivery mechanism should control the rate of release. The ideal release mechanism should be at a constant rate (zero order). However, changing concentration gradients or additive leaching leading to porosity, etc., within the release devices typically mean that the release of the drug varies as a function of time.

Lehmann *et al* (1979). give four advantages of the coating of small drug particles, as opposed to single tablets:

- coated particles will distribute over the stomach and intestine to give a more uniform release and reduce the effects due to local conditions such as pH;
- a drug can be coated with different coatings, or thickness of coating, to give the required release profile;
- disparate active ingredients can be coated individually; and
- the danger of dosage overdose due to coat faults or, alternatively, incomplete release of drug is reduced.

The size of the dosage form may be controlled by factors such as the potency of the drug, and the amount required (although this may be controlled to some extent by the use of either fillers, to enlarge the formulation, or division of the dose into more than one 'packet' to decrease physical size). Duration of release of the drug is a further factor that must be considered (including the transit time of the dosage form through the body, or to the required site of release) as must the means of administration (*eg*, oral or other means, *ie*, parenteral).

Polymers used in sustained release coatings are necessarily biocompatible, and ideally biodegradable. The literature gives examples of both naturally occurring polymers such as Aquacoat® (FMC Corporation, Food & Pharmaceutical Products Division, Philadelphia, USA) (ethylcellulose mechanically spheronised to sub-micron sized, aqueous based, pseudo-latex dispersions), and also synthetic polymers such as the Eudragit® (Röhm Pharma, Weiterstadt.) range of poly(acrylate, methacrylate) copolymers. (Comparisons of aqueous versus solvent cast coatings have been made by Hogan (1982).)

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3.1 Reservoir Devices.

A typical approach to controlled release is to encapsulate or contain the drug entirely (*eg*, as a core [*eg*, see previous Lehmann reference]), within a polymer film or coat (*ie*, microcapsules or spray/pan coated cores). Film coating (with particular reference to polymers and their additives) has been reviewed by Kala *et al.* (1979), whilst microencapsulation has been reviewed by Arshady (3 references: 1989, 1990, & 1990).

The various factors that can affect the diffusion process may readily be applied to reservoir devices (*eg*, the effects of additives, polymer functionality {and, hence, sink-solution pH} porosity, film casting conditions, etc.) and, hence, the choice of polymer must be an important consideration in the development of reservoir devices. Modelling the release characteristics of reservoir devices (and monolithic devices) in which the transport of the drug is by a solution-diffusion mechanism therefore typically involves a

solution to Fick's second law (unsteady-state conditions; concentration dependent flux) for the relevant boundary conditions. When the device contains dissolved active agent, the rate of release decreases exponentially with time as the concentration (activity) of the agent (*ie*, the driving force for release) within the device decreases (*ie*, first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant (zero order) until the device is no longer saturated [deV Naylor (book) and Stannett *et al.* (1979)]. Alternatively the release-rate kinetics may be desorption controlled, and a function of the square root of time.

Transport properties of coated tablets, may be enhanced compared to free-polymer films, due to the enclosed nature of the tablet core (permeant) which may enable the internal build-up of an osmotic pressure which will then act to force the permeant out of the tablet [*eg*, Zentner *et al.* (1985)].

Li & Peck (1989) investigated the effect of deionised water on salt containing tablets coated in poly(ethylene glycol) (PEG)-containing silicone elastomer, and also the effects of water on free films. The release of salt from the tablets was found to be a mixture of diffusion through water filled pores, formed by hydration of the coating, and osmotic pumping. KCl transport through films containing just 10% PEG was negligible, despite extensive swelling observed in similar free films, indicating that porosity was necessary for the release of the KCl which then occurred by 'trans-pore diffusion.' Coated salt tablets, shaped as disks, were found to swell in deionised water and change shape to an oblate spheroid as a result of the build-up of internal hydrostatic pressure: the change in shape providing a means to measure the 'force' generated. As might be expected, the osmotic force decreased with increasing levels of PEG content. The lower PEG levels allowed water to be imbibed through the hydrated polymer; whilst the porosity resulting from the coating dissolving at higher levels of PEG content (20 to 40%) allowed the pressure to be relieved by the flow of KCl.

Li developed methods and equations, which by monitoring (independently) the release of two different salts (*eg*, KCl and NaCl) allowed the calculation of the relative magnitudes that both osmotic pumping and trans-pore diffusion contributed to the release of salt from the tablet. At low PEG levels, osmotic flow was increased to a greater extent than was trans-pore diffusion due to the generation of only a low pore number density: at a loading of 20%, both mechanisms contributed approximately equally to the release. The build-up of hydrostatic pressure, however, decreased the osmotic inflow, and osmotic pumping. At higher loadings of PEG, the hydrated film was more porous and less resistant to outflow of salt. Hence, although the osmotic pumping increased (compared to the lower loading), trans-pore diffusion was the dominant release mechanism. An osmotic release mechanism has also been reported for microcapsules containing a water soluble core [Benita & Donbrow (1982)].

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3.2 Monolithic Devices (Matrix Devices).

Monolithic (matrix) **devices** are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as a dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous

matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network [Singh *et al.* (1968)] (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.

It is common to add a plasticiser (*eg*, a poly(ethylene glycol)), or surfactant, or adjuvant (*ie*, an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticiser may be fugitive, and simply serve to aid film formation [Nakagami *et al.* (1991)] and, hence, decrease permeability - a property normally more desirable in polymer paint coatings). It was noted by Donbrow & Friedman (1975), that the leaching of PEG acted to increase the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity, however, the films retained their barrier properties, not permitting the transport of electrolyte. It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evinced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50% W/W: plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis: the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up. Caffeine, when used as a permeant, showed negative lag times. No explanation of this was forthcoming, but Donbrow noted that caffeine exhibited a low partition coefficient in the system, and that this was also a feature of aniline permeation [Serota *et al.* (1970)] through polyethylene films which showed a similar negative time lag.

Efentakis *et al.* (2 references: Buckton 1991, & 1991). investigated the effects of added surfactants on (hydrophobic) matrix devices. It was thought that surfactant may increase the drug release rate by three possible mechanisms: (i) increased solubilisation, (ii) improved 'wettability' to the dissolution media, and (iii) pore formation as a result of surfactant leaching. For the system studied (Eudragit® RL 100 and RS 100 plasticised by sorbitol, Flurbiprofen as the drug, and a range of surfactants) it was concluded that improved wetting of the tablet led to only a partial improvement in drug release (implying that the release was diffusion, rather than dissolution, controlled), although the effect was greater for Eudragit® RS than Eudragit® RL, whilst the greatest influence on release was by those surfactants that were more soluble due to the formation of 'disruptions' in the matrix allowing the dissolution medium access to within the matrix. This is of obvious relevance to a study of latex films which might be suitable for pharmaceutical coatings, due to the ease with which a polymer latex may be prepared with surfactant as opposed to surfactant-free. Differences were found between the two polymers - with only the Eudragit® RS showing interactions between the anionic/cationic surfactant and drug. This was ascribed to the differing levels of quaternary ammonium ions on the polymer.

Composite devices consisting of a polymer/drug matrix coated in a polymer containing no drug also exist. Such a device was constructed by Bodmeier & Paeratakul (1990)

from aqueous Eudragit® latices, and was found to give zero order release by diffusion of the drug from the core through the shell. Laghoueg *et al.* (1989). similarly produced a polymer core containing the drug, but coated this with a shell that was eroded by the gastric fluid. The rate of release of the drug was found to be relatively linear (a function of the rate limiting diffusion process through the shell) and inversely proportional to the shell thickness, whereas the release from the core alone was found to decrease with time.

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3.3 Other methods of drug carriage and controlled release.

3.3.1 Variations on the theme of microspheres.

Kawashima *et al.* (2 references: both 1992). have described methods for the preparation of hollow microspheres ('microballoons') with the drug dispersed in the sphere's shell, and also highly porous matrix-type microspheres ('microsponges'). The microsponges were prepared by dissolving the drug and polymer in ethanol. On addition to water, the ethanol diffused from the emulsion droplets to leave a highly porous particle. Variation of the ratios of drug and polymer in the ethanol solution gave control over the porosity of the particle, and the drug release properties were fitted to the Higuchi model (2 references: 1961 & 1963).

The hollow microspheres were formed by preparing a solution of ethanol/dichloromethane containing the drug and polymer. On pouring into water, this formed an emulsion containing the dispersed polymer/drug/solvent particles, by a coacervation-type process, from which the ethanol (a good solvent for the polymer) rapidly diffused precipitating polymer at the surface of the droplet to give a hard-shelled particle enclosing the drug, dissolved in the dichloromethane. At this point, a gas phase of dichloromethane was generated within the particle which, after diffusing through the shell, was observed to bubble to the surface of the aqueous phase. The hollow sphere, at reduced pressure, then filled with water, which could be removed by a period of drying. (No drug was found in the water.) A suggested use of the microspheres was as floating drug delivery devices for use in the stomach.

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3.3.2 Pendent devices.

Scholsky and Fitch (1986) developed a means of attaching a range of drugs such as analgesics and antidepressants, etc., by means of an ester linkage to poly(acrylate) ester latex particles prepared by aqueous emulsion polymerisation. These latices when passed through an ion exchange resin such that the polymer end groups were converted to their strong acid form could 'self-catalyse' the release of the drug by hydrolysis of the ester link.

Chafi *et al.* (2 references: 1988 & 1992). cite a number of papers where drugs have been attached to polymers, and also where monomers have been synthesised with a pendent drug attached. The research group have also prepared their own dosage forms in which the drug is bound to a biocompatible polymer by a labile chemical bond [Chafi *et al.* (2 references: 1988 & 1992)]: *eg*, polyanhydrides prepared from a substituted anhydride (itself prepared by reacting an acid chloride with the drug: methacryloyl chloride and the sodium salt of methoxy benzoic acid) were used to form a matrix with a second polymer

(Eudragit® RL) which released the drug on hydrolysis in gastric fluid. Chafi *et al.* (1991) has also described the use of polymeric Schiff bases suitable for use as carriers of pharmaceutical amines.

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3.3.3 Enteric films.

Enteric coatings consist of pH sensitive polymers. Typically the polymers are carboxylated and interact (swell) very little with water at low pH, whilst at high pH the polymers ionise causing swelling, or dissolving of the polymer. Coatings can therefore be designed to remain intact in the acidic environment of the stomach (protecting either the drug from this environment or the stomach from the drug), but to dissolve in the more alkaline environment of the intestine.

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3.3.4 Osmotically controlled devices.

The osmotic pump is similar to a reservoir device but contains an osmotic agent (*eg*, the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane. Such a device, called the **'elementary osmotic pump'**, has been described by Theeuwes (1975). Pressure is generated within the device which forces the active agent out of the device via an orifice (of a size designed to minimise solute diffusion, whilst preventing the build-up of a hydrostatic pressure head which has the effect of decreasing the osmotic pressure and changing the dimensions {volume} of the device). Whilst the internal volume of the device remains constant, and there is an excess of solid (saturated solution) in the device, then the release rate remains constant delivering a volume equal to the volume of solvent uptake.

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3.3.5 Electrically stimulated release devices.

Yuk *et al.* (1992). prepared monolithic devices using polyelectrolyte gels which swelled when, for example, an external electrical stimulus was applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile.

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3.3.6 Hydrogels.

Hydrogels find a use in a number of biomedical applications, in addition to their use in drug matrices (*eg*, soft contact lenses, and various 'soft' implants, etc.) [Pedley *et al.* (1980), and Ratner & Hoffman (1976)].

Adapted from: Modification of the Permeability of Polymer Latex Films., Nottingham Trent University PhD Thesis, 1995.

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